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CASE REPORT

HaNDL syndrome presenting with neuropsychological symptoms and severe papilledema: A case report

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SUMMARY

HaNDL is abbreviated from the definition of "The syndrome of transient Headache and Neurologic Deficits with cerebrospinal fluid Lymphocytosis." The syndrome consists of symptoms and signs characterized by headache, transient neurological deficits, and lymphocytic pleocytosis in the cerebrospinal fluid (CSF). The clinical presentation may resemble some serious neurological disorders, including stroke and viral encephalitis, and may mimic a migraine attack with aura. In this article, a case of a 21-year-old female patient who presented to the emergency department with complaints of dysphasia, somnolence, and agitation following a migraine attack is presented. Grade 4 papilledema was detected on fundus examination; lymphocytic pleocytosis and protein elevation were found in the CSF examination, and the diagnosis was defined as HaNDL syndrome.

Keywords: HaNDL syndrome; migraine; papilledema.

Introduction

HaNDL syndrome, previously referred to as "pseudomigraine with lymphocytic pleocytosis" and "migraine with cerebrospinal pleocytosis," is a rare, benign, and self-limiting condition.[1,2]

According to the International Classification of Headache Disorders, 3rd edition (ICHD-3) revised in 2018, the diagnostic criteria for HaNDL syndrome are:

- A: Migraine-like headache episodes fulfilling criteria B and C
- B: One or more transient neurological symptoms (hemiparesthesia, dysphasia, hemiparesis) lasting more than 4 hours, associated with lymphocytic pleocytosis (>15 cells/μL) in cerebrospinal fluid (CSF), with negative cultures and serologies
- C: There is a close temporal relationship between the onset or worsening of headache and transient neurological symptoms and the presence of CSF pleocytosis (or such symptoms lead to the detection of CSF pleocytosis), and/or the resolution of headache and neurological symptoms occurs in parallel with the normalization of CSF findings.
- D: Not better accounted for by another ICHD-3 diagnosis.[2] HaNDL is a diagnosis of exclusion. Differential diagnoses include stroke, migraine with aura, epilepsy, encephalitis, meningitis, neuroborreliosis, neurosyphilis, neurobrucellosis, mycoplasma infection, reversible posterior leukoencephalopathy syndrome (RPLS), granulomatous and neoplastic arachnoiditis, and central nervous system (CNS) vasculitis. Symptoms generally resolve spontaneously within three months.[2–4]

The presented case of HaNDL syndrome is of particular interest as it manifested with neuropsychological symptoms superimposed on an active migraine attack.

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Case Report

Signed consent was obtained from the patient for the publication of this article. A 21-year-old female presented to the emergency department with headache, altered consciousness, somnolence, nausea, and vomiting. Vital signs were within normal limits. Neurological examination revealed confusion, agitation, dysphasia, and no response to simple commands. No focal motor deficits were observed. The patient was non-cooperative for sensory examination; bilateral plantar skin reflexes were negative. Fundus examination revealed bilateral grade 4 papilledema. There was no sign of meningeal irritation. The neurological symptoms resolved within hours.

Three days earlier, the patient had experienced a similar episode. The headache was described as pulsating, accompanied by nausea, vomiting, photophobia, and phonophobia. On the second day of that attack, she developed dysphasia, weakness in the left arm and leg, gait disturbance, nonsensical speech, and inappropriate laughter—all of which resolved within 7–8 hours.

The patient had a known history of migraine without aura, occurring 2–3 times per month. Family history was unremarkable.

Lumbar puncture revealed an opening pressure of 270 mmH_2O. CSF analysis showed protein 93 mg/dL, glucose ratio consistent with serum glucose, and 140/mm^3 lymphocytic pleocytosis (100%). Gram stain and herpes simplex virüs (HSV)-1/2 PCR were negative; no growth was observed in cultures.

Serum C-reactive protein (CRP) was 0.48 mg/L, erythrocyte sedimentation rate (ESR) was 6 mm/hour, and white blood cell count was 5.902×10^3/µL. D-dimer level was 0.3 µg/mL. The serum vasculitis panel was within normal limits. Serologic tests for Brucella, HIV (anti-HIV), hepatitis B surface antigen (HBsAg), and syphilis were all negative. Contrast-enhanced brain magnetic resonance imaging (MRI), magnetic resonance venography (MRV), diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) mapping were all within normal limits.

Due to grade 4 papilledema secondary to increased intracranial pressure and elevated CSF opening pressure, the patient was started on acetazolamide treatment at a dose of 1500 mg/day. In the patient's follow-up, the drug dose was reduced in parallel with the improvement of papilledema and was discontinued at the end of the 2nd month. Following two months of treatment, fundoscopic examination returned to normal, and both visual acuity and visual field testing were within normal limits. On lumbar puncture (LP), the opening cerebrospinal fluid (CSF) pressure was measured as 170 mmH_2O. CSF protein level was 34 mg/L, and the glucose concentration was proportional to the simultaneous blood glucose level. Cell analysis revealed 10 lymphocytes/mm^3, which was not considered significant by the infectious diseases specialist. No bacteria were observed on Gram stain, and there was no growth in CSF culture.

Discussion

HaNDL is a rare disorder characterized by headache, transient neurological symptoms, and lymphocytic pleocytosis in the CSF. Clinically, it most commonly mimics stroke and viral encephalitis.[5] It generally occurs between the second and fourth decades of life.[6] Since certain viral infections can cause transient neurological deficits and lymphocytic pleocytosis in the CSF, a thorough investigation for infectious, particularly viral, etiologies is essential in suspected HaNDL cases to meet diagnostic criteria.[7] Although the exact etiopathogenesis of the syndrome is not fully understood, several hypotheses have been proposed to explain its pathophysiology. Studies investigating a possible association between HaNDL syndrome and acute ischemic stroke have found that despite prolonged neurological deficits, patients' diffusion-weighted MRI scans were normal.[8] However, rare cases demonstrating diffusion restriction have been reported in the literatüre.[9] Approximately 25% of cases had a history of a virallike infection about three weeks prior to syndrome onset,[6] suggesting the possibility that HaNDL may occur secondary to a viral infection.[1] In a recent HaNDL case report, diffusion restriction in the corpus callosum on MRI and detection of Epstein–Barr virus (EBV) DNA in the cerebrospinal fluid were documented.

Researchers have hypothesized that a post- or para-infectious immune-mediated mechanism may be triggered, contributing to cerebral vascular injury; vasoconstriction is thought to play a role in the pathogenesis of transient neurological symptoms and headache.[10] However, to date, no definitive association with any specific virus has been established.[1] Another hypothesis proposes that a cortical spreading depression-like neuronal activity induces leptomeningeal vasculitis via an inflammatory mechanism, leading to headache and neurological deficits.[11] Since approximately 26% of patients have a history of migraine, some authors suggest that the pathophysiology may be related to migraine.[1,3,7,12,13] Although viral causes, stroke, and migraine have been considered as possible etiologies, the exact cause remains unclear.[14]

The presented case was defined as HaNDL syndrome because it met the diagnostic criteria. The patient was 21 years old, which is within the commonly reported age range in the literature. The described headache was accompanied by nausea, vomiting, photophobia, and phonophobia. The patient described the headache as one of her usual migraine attacks and had a history of migraine. Considering these data, it was hypothesized that the pathophysiology may be related to migraine.

In HaNDL syndrome, most patients describe a severe, throbbing headache unlike any they have experienced before. The pain is typically bilateral and lasts from one hour to one week. Photophobia and phonophobia may accompany the headache.[6,15] Transient neurological deficits can occur before or during the headache.[6] Neurological deficits in approximately 80% of patients are transient and involve a single hemisphere. Findings are consistent with right hemispheric involvement in 74% of cases. The duration of neurological deficits ranges from 5 minutes to 3 days. The most common symptoms are sensory deficits (70%), followed by aphasia (66%), hemiparesis (42%), and visual symptoms (18%). The most frequent combination is motor aphasia with sensory and motor symptoms affecting one side of the body.[6]

Increased intracranial pressure and papilledema may accompany HaNDL syndrome. As in other diseases causing papilledema, these patients may develop permanent visual sequelae.[16] In the presented case, neurological deficits appeared on the second day of headache. The first attack showed left hemiparesis, the most common finding reported in the literature; the second attack manifested with aphasia, altered consciousness, and agitation. Papilledema was also noted on neurological examination alongside the neurological deficits.

In HaNDL syndrome, brain MRI is typically normal; however, susceptibility-weighted imaging (SWI) may reveal focal leptomeningeal contrast enhancement.[17] On computed tomography (CT), single-photon emission computed tomography (SPECT), and perfusion imaging, areas of hypoperfusion can be observed without evidence of vascular occlusion.[7]

In the present case, during the differential diagnosis process, the presence of papilledema in addition to neurological deficits initially raised suspicion of cerebral venous thrombosis (CVT). To exclude this, diffusion MRI, brain MRI, and MR venography (MRV) were performed. No diffusion restriction, thrombosed veins, or dural sinus thrombosis were observed, and no hemorrhagic infarct was detected. Given the normal brain MRI and MRV findings and the rapid resolution of clinical symptoms, the diagnosis of CVT was ruled out.

Due to lymphocytic pleocytosis and elevated protein levels in the CSF, a viral infection was considered a possible cause, and viral etiologies were investigated. CSF HSV PCR testing was negative. There was no recent history of infection. The patient had no fever or signs of meningeal irritation during the attacks. Laboratory parameters, including erythrocyte sedimentation rate (ESR), CRP, D-dimer, and white blood cell count, were within normal limits. Contrast-enhanced brain MRI showed no meningeal or parenchymal enhancement. As the neurological deficits were transient, the diagnoses of encephalitis and meningitis were excluded.

The presence of papilledema along with headache and elevated CSF opening pressure on lumbar puncture initially suggested a diagnosis of idiopathic intracranial hypertension (IIH). However, the presence of additional neurological symptoms and CSF analy-

sis showing both elevated protein and lymphocytosis ruled out IIH. Tests for systemic brucellosis, syphilis, and vasculitis were negative. There was no history of tick bite suggestive of neuroborreliosis. The case was ultimately diagnosed as HaNDL syndrome. Considering the self-limiting nature of HaNDL, no therapeutic intervention was performed other than measures to reduce intracranial pressure. After approximately two months of acetazolamide treatment, fundoscopic examination normalized and the patient recovered without sequelae.

Conclusion

A striking feature of the presented case was the emergence of neurological deficits following a two-day episode of migraine without aura. In addition, the presence of papilledema progressing to retinal hemorrhages and the presentation of neuropsychological findings such as inappropriate laughter make this case different from others in the literature.

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